

5 What is claimed is:

1. A composition comprising a peptide with an amino acid sequence having two tyrosine (Y) residues and a lysine (K) residue, wherein in a complex of the peptide with an MHC class II HLA-DR2 protein involved in modulation of an immune response, the residues
10 in the amino acid sequence corresponding to: (i) tyrosines located at P1 and P4 positions; and (ii) lysine located at a P5 position which contacts a T cell receptor protein.

2. A composition comprising a peptide with an amino acid sequence having at least a tyrosine (Y) residue, a valine residue (V), and a lysine (K) residue, wherein in a
15 complex of the peptide with an MHC class II HLA-DR2 protein involved in modulation of an immune response, the residues in the amino acid sequence corresponding to: (i) valine located at a P1 position; (ii) tyrosine located at a P4 position; and (iii) lysine located at a P5 position which contacts a T cell receptor.

20 3. The composition of claims 1 or 2, the sequence further comprising a lysine (K) residue at a P-1 position.

4. The composition of claims 1 or 2, wherein the sequence of the peptide further includes a plurality of alanine (A) residues at positions which are to the carboxy-terminal side
25 of the lysine residue at P5.

5. The composition of claims 1 or 2, wherein the peptide is substantially pure.

6. A composition according to claims 1 or 2, further comprising an additional
30 therapeutic agent.

7. The composition of claim 6, wherein the additional therapeutic agent is selected from the group consisting of an interferon and a random heteropolymer of amino acids.

35 8. The composition of claim 1 or 2, wherein the peptide is synthetic.

9. A composition comprising a synthetic peptide, wherein the peptide has an amino acid sequence having a greater inhibitory activity for binding to the antigen binding

5 groove of an MHC class II HLA-DR2 protein associated with multiple sclerosis, than a
reference material selected from the group of: an immunodominant epitope from myelin basic
protein (MBP), the epitope comprising MBP residues 85-99 ENPVVHFFKNIVTPR as shown
in SEQ ID NO: 1; and a randomly polymerized amino acid heteropolymer having amino
acids, tyrosine, alanine, glutamic acid, and lysine (Copaxone®), the composition further
10 capable of inhibiting proliferation of an MBP-specific T cell.

10. The composition of claim 9, wherein the greater inhibitory activity is at least
10%.

15 11. The composition of claim 9, wherein the greater inhibitory activity is at least
20%.

12. The composition of claim 9, wherein the peptide is about 5 to about 100 amino
acids in length.

20 13. The composition of claim 9, wherein the peptide is about 5 to about 25 amino
acids in length.

14. The composition of claim 9, wherein the peptide is about 5 to about 15 amino
25 acids in length.

15. The composition of claim 9, the peptide further comprising at least one non-
naturally occurring amino acid, in a location in the sequence and in an amount sufficient to
inhibit proteolytic degradation of the peptide in a subject, in comparison with a peptide
30 identical in sequence and consisting of naturally occurring amino acid residues.

16. The composition of claim 9, further comprising at least one non-naturally
occurring amino acid, in a location in the sequence and in an amount sufficient to increase the
affinity for the antigen binding groove of the MHC class II HLA-DR2 protein, in comparison
35 with a peptide identical in sequence and consisting of naturally occurring amino acid residues.

17. The composition of claim 9, comprising a plurality of copies of the peptide as a
monomer unit of an oligomer, each monomer unit being joined by a flexible linker.

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18. The composition of claim 17, wherein the oligomer is a homo-oligomer.

19. The composition of claim 17, wherein the oligomer is a hetero-oligomer.

10 20. The composition of claim 11, further comprising the presence in the sequence of at least one proline residue.

21. The composition of claim 20, wherein the at least one proline residue is present proximal to at least one of carboxy- and amino-termini of the sequence.

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22. The composition of claim 21, wherein at least one proline is present within four residues of at least one of carboxy and amino termini.

20 23. The composition of claim 15, wherein at least one non-naturally occurring amino acid is the presence of at least one D-amino acid within four residues of at least one of the carboxy-terminal and amino-terminal.

24. The composition of claim 11, further comprising at least one non-peptide bond.

25 25. The composition of claim 15, wherein the non-naturally occurring amino acid is a substitution of at least one alanine (A) in the sequence with a peptidomimetic compound selected from the group consisting of: Tic, which is tetrahydroisoquinoline-(S)-3-carboxylic acid); Thiq, which is tetrahydroisoquinoline-(S)-1-carboxylic acid); Disc, which is (dihydroisoindeole-(S)-2-carboxylic acid); C(Acm), which is acetamido-methyl-Cys; C(Prm), which is propylamidomethyl-Cys; C(Ace), which is acetyl-Cys; MePhg, which is methylphenyl-Gly; and Nva, which is norvaline.

26. The composition of claim 24, wherein the non-peptide bond is selected from the group consisting of a peptide nucleic acid bond and a phosphorothioate bond.

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27. The composition of claim 24, wherein the amino acid modification is N-methylation of a peptide backbone nitrogen.

5 28. A composition comprising a synthetic peptide having an amino acid sequence
selected from the group consisting of:

AAEAYKAYKAAAAAA (SEQ ID NO: 60),
EAAAYKAYKAAAAAA (SEQ ID NO: 63),
EAAKYEAYKAAAAAA (SEQ ID NO: 64),
10 EKAKYEAYKAAAAAA (SEQ ID NO: 65),
EAKKYEAYKAAAAAA (SEQ ID NO: 66),
AKKEYAEYKAAAAAA (SEQ ID NO: 67),
EAPAYKAYKAAAAPA (SEQ ID NO: 83),
EAPKYEAYKAAAAPA (SEQ ID NO: 84),
15 EKPKYEAYKAAAAPA (SEQ ID NO: 85),
EAPKYEAYKAAAAPA (SEQ ID NO: 86),
AKPEYAEYKAAAAPA (SEQ ID NO: 87),
APEKAKYEAYKAAAAAA (SEQ ID NO: 88),
APEKAKYEAYKAAAAAPA (SEQ ID NO: 89),
20 EKAKYEAYKAAAAAPA (SEQ ID NO: 90),
EKPKFEAYKAAAAPA (SEQ ID NO: 91),
EKAKYEAYKAAAAAA (SEQ ID NO: 92),
EKPKVEAYKAAAAPA (SEQ ID NO: 93),
EKPKKEAFKAAAAPA (SEQ ID NO: 94),
25 EKAKFEAFKAAAAAA (SEQ ID NO: 95),
APEKAKFEAFKAAAAPA (SEQ ID NO: 96),
APEKAKFEAYKAAAAPA (SEQ ID NO: 97),
EAPKFEAYKAAAAPA (SEQ ID NO: 98), and
EAPKVEAYKAAAAPA (SEQ ID NO: 99).

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29. The composition of claim 28, wherein the peptide is substantially pure.

30. The composition of claim 28, further comprising substitution of an alanine (A)
or lysine (K) at position P4 by an amino acid selected from the group consisting of tyrosine
35 (Y), phenylalanine (F), methionine (M), valine (V), isoleucine (I) and leucine (L).

31. The composition of claim 28, further comprising substitution of a tyrosine (Y)
in the P1 position by a valine (V).

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32. The composition of claim 28, wherein the peptide comprises an oligomer having a plurality of monomer units having the amino acid sequence of the synthetic peptide, the units joined by a flexible linker.

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33. A method for reducing demyelination of cells in a subject, the method comprising administering to the subject a composition as shown in claim 28.

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34. A method for obtaining a synthetic peptide having inhibitory activity for binding of an immunodominant epitope of multiple sclerosis (MS) to an MHC class II protein associated with MS, the method comprising:

designing a plurality of peptide sequences, wherein each peptide comprises a sequence of amino acids having a charge, size, and order within the sequence such that the peptide is capable of occupying features of an antigen binding site of an MHC class II protein associated with multiple sclerosis (MS); and

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assaying each of the plurality of peptides for affinity for the MHC class II protein, to determine the amount of the peptide having inhibitory activity for binding of a reference compound to the MHC class II protein, wherein a lower amount of peptide able to inhibit the extent of binding compared to the reference compound indicates a greater inhibitory activity of the peptide for inhibiting binding of an immunodominant epitope of multiple sclerosis (MS) to an MHC class II protein associated with MS.

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35. A method for obtaining a synthetic peptide having inhibitory activity for proliferation of cells of a T cell line, the T cells restricted to an immunodominant epitope of multiple sclerosis (MS), the method comprising:

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designing a plurality of peptide sequences, wherein each peptide comprises a sequence of amino acids having a charge, size, and order within the sequence such that the peptide is capable of occupying features of an antigen binding site of an MHC class II protein associated with MS; and

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assaying each of the plurality of peptides for an amount that has ability to inhibit proliferation of the T cells in comparison to a reference compound, wherein a lower amount of peptide able to inhibit the proliferation of the cells compared to the reference compound indicates a greater inhibitory activity of the peptide for inhibiting the T cells restricted to an immunodominant epitope of MS.

5 36. The method of claims 34 or 35, wherein the reference compound is selected from a group consisting of Copaxone® and a peptide comprising a sequence of amino acids at positions 85-99 of myelin basic protein (MBP) as shown in SEQ ID NO: 1.

10 37. The method of claims 34 or 35, further comprising: measuring an ability of each of the plurality of peptides to inhibit presentation of the reference compound to HLA restricted T cells.

15 38. The method of claims 34 or 35, wherein designing a plurality of peptide sequences having a charge, a size, and an order within the sequence is choosing amino acids to occupy positions in the sequence of that peptide capable of contacting the antigen binding P1 and P4 pockets of the MHC class II protein associated with MS, corresponding to locations in the MBP 85-99 peptide amino acid sequence at residues 89 and 92, respectively.

20 39. The method of claim 38, further comprising selecting the amino acids contacting the P1 and P4 pockets from the group consisting of hydrophobic amino acids.

25 40. The method of claim 39, wherein the hydrophobic amino acids are selected from the group consisting of a tyrosine (Y), a valine (V), a phenylalanine (F), a methionine (M), an isoleucine (I), and a leucine (L).

 41. The method of claim 38, wherein the hydrophobic amino acids contacting the P4 pocket are selected from the group consisting of a tyrosine (Y) and a phenylalanine (F).

30 42. The method of claim 38, wherein the amino acid contacting the P1 pocket is valine (V).

 43. The method of claim 39, wherein the amino acid in the P5 position is a lysine (K).

35 44. The method of claims 34 or 35, wherein in comparing the affinity of each of the plurality of peptides, the method further comprises providing a reference compound having a detectable modification.

5 45. The method of claim 44, wherein the modification is selected from the group of compounds which are radioactive, antigenic, biotinylated, fluorescent, photometric, and have a high affinity for an immobilized ligand.

10 46. The method of claim 34, wherein after determining the concentration of the peptide able to inhibit an extent of binding of the test compound to the MHC class II protein associated with multiple sclerosis, the method further comprises measuring an amount of proliferation of a DR2-restricted cell line of T cells exposed to the complex of the peptide with the MHC class II protein.

15 47. The method of claim 46, wherein measuring the amount of proliferation further comprises determining an amount of IL-2 secretion by the T cells.

20 48. The method of claim 47, wherein determining the amount of IL-2 secretion further comprises assaying culture fluid of the T cells for ability to support growth of IL-2 dependent cytotoxic T-cell interleukin-dependent lymphocytes (CTLL).

25 49. A method of treating a subject having a demyelinating condition, comprising: providing to the subject a composition capable of inhibiting binding of myelin basis protein (MBP) peptide to purified recombinant MHC class II DR2 molecules, wherein the composition is a peptide that comprises an amino acid sequence selected from the group consisting of:
AAEAYKAYKAAAAAA (SEQ ID NO: 60), EAAAYKAYKAAAAAA (SEQ ID NO: 63),
EAAKYEAYKAAAAAA (SEQ ID NO: 64), EKAKYEAYKAAAAAA (SEQ ID NO: 65),
EAKKYEAYKAAAAAA (SEQ ID NO: 66), AKKEYAEYKAAAAAA (SEQ ID NO: 67),
EAPAYKAYKAAAAPA (SEQ ID NO: 83), EAPKYEAYKAAAAPA (SEQ ID NO: 84),
30 EAPKYEAYKAAAAPA (SEQ ID NO: 86), AKPEYAEYKAAAAPA (SEQ ID NO: 87),
APEKAKYEAYKAAAAAA (SEQ ID NO: 88), APEKAKYEAYKAAAAPA (SEQ ID NO: 89), EKAKYEAYKAAAAPA (SEQ ID NO: 90), EKPKFEAYKAAAAPA (SEQ ID NO: 91), EKPKVEAYKAAAAPA (SEQ ID NO: 93), EKAKFEAFKAAAAAA (SEQ ID NO: 95), APEKAKFEAFKAAAAPA (SEQ ID NO: 96), and APEKAKFEAYKAAAAPA
35 (SEQ ID NO: 97), wherein the subject having a demyelinating condition is treated.

5 50. The method of claim 49, wherein the demyelinating condition is selected from the group consisting of a post-viral encephalomyelitis, a post-vaccine demyelinating condition, a multiple sclerosis, and a side effect of administering an anti-TNF agent.

10 51. The method of claim 49, wherein the MBP peptide comprises MBP residues 85-99 as shown in SEQ ID NO: 1.

15 52. The method of claim 49, wherein the peptide further inhibits proliferation of autoantigen-specific HLA-DR2-restricted T-cell clones.

15 53. The method of claim 49, wherein the amino acid sequence of the peptide further comprises at least one amino acid analog substituted for an amino acid.

20 54. The method of claim 49, wherein the amino acid sequence of the peptide comprises at least one peptide bond analog.

20 55. The method of claim 49, further comprising formulating the composition in a pharmaceutically acceptable carrier.

25 56. The method of claim 49, further comprising formulating the composition as a unit dose.

 57. The method of claim 49, wherein the MHC class II DR2 molecules are of a genotype associated with multiple sclerosis.

30 58. The method of claim 57, wherein the MHC class II DR2 molecules are selected from the group consisting of DRB1*1501 and DRB1*1602.

35 59. A kit comprising at least one container having a peptide capable of inhibiting binding of an immunodominant epitope of myelin basic protein to an MHC class II DR2 protein, and instructions for use.

 60. The kit of claim 59, wherein the peptide is substantially pure.

